Predicting the long-term outcome of bacterial meningitis in childhood

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Summary

Samenvatting

SUMMARY: PREDICTING THE LONG-TERM OUTCOME OF BACTERIAL MENINGITIS IN CHILDHOOD

INTRODUCTION

Bacterial meningitis (BM) is a serious infection of the central nervous system (CNS) that affects about 5 per 100,000 Dutch children each year. In about 15% of the children who survive BM, severe sequelae such as hearing loss, motor problems, seizures and mental retardation occur. More subtle adverse outcomes such as cognitive, academic and behavioral problems are present in over 20-30%. In recent years, the group of Koomen and Van Furth *et al*. explored the incidence of post-BM hearing loss and academic and behavioral problems and developed two clinical prediction models: one to identify children at risk of developing hearing loss and one for the prediction of academic or behavioral limitations after BM.
This thesis focuses on a broad range of long-term sequelae after childhood BM in general and on the external validation and updating of these clinical prediction models in particular.

PREDICTION OF OUTCOME

Chapter 2 presents a systematic review of prognostic studies summarizing the evidence of prognostic factors regarding mortality and long-term sequelae in developed en developing countries. The following prognostic factors for the prediction of mortality or sequelae after BM during childhood were found: complaints >48 hours before admission, coma/impaired consciousness, (prolonged duration of) seizures, (prolonged) fever, shock, peripheral circulatory failure, respiratory distress, absence of petechiae, causative pathogen *Streptococcus pneumoniae*, young age, male gender, several cerebrospinal fluid (CSF) parameters and low white blood cell (WBC) count. Due to limited quality and heterogeneity meta-analysis was not possible, and therefore findings must be interpreted and used cautiously. This emphasizes the need for additional well-conducted prognostic studies on this subject.

In **Chapter 3** the clinical prediction model for hearing loss was successfully validated in a new, independent cohort of childhood BM survivors. Children at risk for hearing loss after childhood BM can be identified with the clinical prediction model. Independent risk factors included in the model are: duration of symptoms prior to admission, petechiae, CSF glucose level, *S. pneumoniae* as a causative pathogen and ataxia as a symptom. The model is not a replacement for good audiological follow-up protocols, but is a valuable adjuvant. It can be used in areas with scarce availability of adequate follow-up and support in case of auditory deficits where it can facilitate selection of the group of children that urgently needs hearing evaluation. But, additional local validation and probably updating of the prediction model is essential.

Chapter 4 describes the addition of host genetic variants to the prediction rule validated in **Chapter 3**, to find out if further improvement of prediction can be achieved. Although addition of genetic risk factors did not significantly improve the clinical prediction model for hearing loss after BM, addition of *TLR9*-1237 SNPs and the combination of *TLR2*+2477 and *TLR4*+896 SNPs improved the clinical prediction model. Genetic factors might contribute to a good clinical prediction model, but to optimize the effect they must be incorporated in the development of the model.

Chapter 5 describes the unsuccessful external validation of the clinical prediction model for academic or behavioral limitations after BM in childhood. The model is not suitable for implementation in clinical practice. The combined outcome measure academic or behavioral problems should be disentangled and two new prediction models must be developed: one for academic and one for behavioral problems.

In **Chapter 6** the effect of pneumococcal vaccination on the generalizability of the two prediction rules is explored by simulation of this vaccination in the development cohorts. The simulated situation of a vaccinated population with a seven-valent conjugate vaccination against *S. pneumoniae* resulted in good reproducibility of both the prediction model for hearing loss and for academic or behavioral limitations after BM. Performance of the prediction rules remained good in the further identical population as they were developed in. It is assumed that the prediction rules will be applicable in the reality of a vaccinated population. But vaccination does not provide full coverage and serotype replacement might occur. Therefore the prediction models must be updated in a vaccinated cohort.

BEHAVIORAL PROBLEMS AFTER BACTERIAL MENINGITIS IN CHILDHOOD

In **Chapter 7** the emotional and behavioral sequelae of childhood BM are further investigated. The diagnostic capabilities of the Strength and Difficulties Questionnaire (SDQ) is compared with the "gold standard", the Child Behavior Checklist (CBCL). The SDQ proved to be an acceptable screening tool for emotional and behavioral problems of BM survivors.
Then, the increased incidence of behavioral problems in BM survivors is described with the use of the SDQ. An increased prevalence of problems in school age BM survivors was found in multiple domains of emotional and behavioral functioning.

BACTERIAL MENINGITIS AND NEUROIMAGING

In **Chapter 8** the hypothesis that BM can lead to structural differences in the brain was tested with cerebral Magnetic Resonance Imaging (MRI) scans. Based on experimental animal studies and case series in adults it was hypothesized that children with a history of childhood BM without major sequelae but with proven learning or behavioral problems may have atrophy of the hippocampus. Therefore there was a special focus on possible decrease in volume of the hippocampus, but differences in other regions of the brain were investigated as well. However, this study found no differences in hippocampal volume between BM survivors and their controls. There were also no anatomical differences in other regions of the brain. While structural differences were not found, functional imaging (e.g. fMRI or Single Photon Emission Computed Tomography (SPECT)) should be the next step in research.

CONCLUSIONS AND FUTURE PERSPECTIVES

Chapter 9 concludes this thesis with a general discussion and ideas about future perspectives. First conclusion is that research on the long-term effects of childhood BM is and stays essential. Further, prediction models have the ability to be a valuable additive in management and follow-up of many diseases in general and of BM in particular, and they can support decision making. But it is vital to develop strong, usable models for daily practice. An ongoing process of validation, updating and impact evaluation in many different settings and global regions must confirm and maintain the quality.

For the prediction model for hearing loss after BM this means the implementation in Dutch follow-up protocols for hearing evaluation, an update in a recent cohort with children vaccinated according to current guidelines and evaluation of impact after some time.

The prediction model for academic or behavioral limitations needs to be redeveloped. This model must be split in two, creating a model for academic limitations and one for behavioral problems. Genetic factors should be included from the beginning, and the strongest genetic factors may be found with new sequencing techniques and genome-wide association studies (GWAS).

To reach optimal performance and generalizability of the models all these steps should be performed in prospective constructed cohorts with large sample sizes. With the present low incidence of childhood BM in western countries international collaboration is the only way to achieve these goals.

Where it comes to neuroimaging, the future lies in higher spatial resolution of MRI and in functional imaging, like SPECT and fMRI.